REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

Claims 1, 28-32 and 100-106 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Constancis et al. This rejection is respectfully traversed.

Constancis is said to meet the two elements of the claims: (1) a polymeric moiety having not more than 10 different monomers, and (2) at least one non-terminal thiol group. The Official Action asserts that, with respect to our argument that Constancis fails to teach "mucoadhesive" polymers as claimed, "the mucoadhesive property of the polymer would be a functional property inherent to the elements of the polymer." Page 3. With respect to the previously submitted Declaration, it was not found persuasive. According to the Official Action, while the Declaration concludes that the Constancis polymers would not adhere to the mucosa with the same strength as those claimed, there is no evidence in this regard. Moreover, since the claims are not limited to any particular mucoadhesive strength, the Examiner asserts that the Constancis polymers "must possess at least some degree of mucoadhesion," since they meet the limitations of the claims. Moreover, it is asserted that the compositions of Constancis are taught to be used in dental surgery "where their use is primarily for their cohesiveness or adhesive properties (col. 4, lines 34-40, col. 5, lines 5-14)," and concluded that "[s]ince mouth essentially is covered by mucus, the polymer of Constancis are viewed to possess mucoadhesive properties." Page 3. These assertions are in error.

Applicant maintains that the polymers of Constancis are *not* mucoadhesive. To substantiate this position, Applicant prepared and tested all polymers mentioned in Constancis for which the synthesis is described therein. These experiments are shown in the enclosed Second Declaration of Dr. Bernkop-Shnürch. These polymers were all synthesized and their chemical structure confirmed by ^{1}H-NMR, IR, and MALDI-TOF MS. The crosslinked Polymer 2, which is crosslinked by cystine dimethyl ester and shown in examples 6 and 9, was chosen as the most hydrophilic polymer, *i.e.*, the polymer with the methyl esters has a slightly higher chance of being mucoadhesive. This polymer was chosen as more likely to be mucoadhesive than the polymer crosslinked by cystine diethyl ester, as shown in examples 7 and 10.

The mucoadhesive properties of these polymers were determined according to the method established by Ch'ng et al. (J. Pharm. Sci. 74 (1985) 399-405), carried out as described in Bernkop-Schnürch et al. (Pharm. Res. 16 (6) 1999, 876-881), representing exactly the same method as described in example 1 of the instant application. The results of these mucoadhesion studies are summarized in the following table:

Tested Polymer	Total work of adhesion (TWA) (means ±S.D.; n=3)
Polymer 1 (according to example 1)	has no thiol groups at all
Polymer 2 (according to example 3)	has no thiol groups at all
Reduced Polymer 2 (according to example 4)	0.9 ±1.6 μJ
Crosslinked Polymer 2 (according to example 6)	has no thiol groups at all
Reduced crosslinked Polymer 2 (according to example 8)	0.7 ±1.2 μJ
Reduced crosslinked Polymer 2 with hydrolysed ester functions (according to example 9)	none [1]

[1] Test discs dissolved so rapidly in the buffer solution, that no adhesion at all could be measured.

As concluded by Dr. Bernkop-Schnürch, these tests evidence that none of the polymers described by Constancis displayed statistically significant mucoadhesive properties. If an inert and completely not mucoadhesive material was tested, similar results would have been obtained. The results are in good agreement with the generally accepted theory about criteria, which have to be fulfilled by a polymer in order to be mucoadhesive (e.g. G. Hunt, P. Kearney and I. Kellaway, *Mucoadhesive polymers in drug delivery systems,* in Drug Delivery Systems, Johnson, P. and Lloyd-Jones, J.G. (eds.) Ellis Horwood, New York (1987)). *See,* Second Bernkop-Schnürch Declaration, Paragraph 28.

In view of the above and the enclosed Declaration, the polymers of Constancis do not inherently possess the property of being mucoadhesive. Constancis thus fails to disclose or even suggest the instantly claimed invention. Constancis in no way discloses or suggests mucoadhesive properties as claimed herein. Contrary to the assertion in the Official Action, the mucoadhesive property of the polymer is *not* a "functional property

inherent to the elements of the polymer." Page 3. Constancis is *not* anticipatory to the scope of the rejected claims. The "central issue" identified on page 4 of the Official Action is said to be whether Constancis' polymer provides mucoadhesive properties. Applicant has shown that Constancis' polymers do *not* possess such properties. This Declaration substantiates the conclusion in Dr. Bernkop-Schnürch's prior Declaration that the Constancis polymers would *not* adhere to the mucosa with the same strength as mucoadhesive polymers of the instant claims and that the Constancis polymers do not fulfill the minimal criteria to be mucoadhesive. As requested by the Official Action, evidence of this assertion is now provided. *See,* Bernkop-Schnürch Declaration, Paragraphs 27-29.

Moreover, it is asserted in the Official Action that the use of the polymers of Constancis in dental surgery shows that they are mucoadhesive. This assertion is in error. The properties of an adhesive in dental surgery are not the same as a mucoadhesive. The principle of binding of bioadhesives is based, according to Constancis, on a diffusion process of the monomers/oligomers into the tissue followed by a stabilizing polymerization process via oxidation of the thiol groups. This is similar to the principle used in other "super glues," such as glues based on cyanoacrylates which diffuse into surfaces and subsequently polymerize. The goal for bioadhesion is to achieve a very tight and strong connection of the bioadhesive with a given cell or tissue surface or to achieve a strong connection between cell or tissue surfaces. The "goal" for the compounds of Constancis is thus to adhere directly to the tissue.

"Mucoadhesion" is based on a different scientific concept. A tight binding of a polymer molecule to the (tissue) surface adjacent to the mucus is not desired for a mucoadhesive polymer. Mucoadhesive polymers should instead specifically bind to the mucus layer above the tissue in these areas. The "goal" of bioadhesives and mucoadhesives thus differ and are based on different scientific principles.

In view of the above, as well as the Declaration submitted herewith, withdrawal of the rejection of record under §102(b) over Constancis is respectfully requested. Such action is believed to be in order.

Claims 1, 28, 29 and 31-38 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Moens. This rejection is respectfully traversed.

The grounds are basically the same as set forth above with respect to Constancis, *i.e.*, that the reference discloses thiol-containing polymers including polycysteine and thus allegedly anticipates the claimed invention. As shown *supra* and in the Declaration submitted herewith, simply because a polymer includes thiol group and polycysteine, it is not necessarily a mucoadhesive polymer as claimed.

The sole disclosure of Moen cited is:

> Hydroxy containing polymers, e.g. polyvinyl alcohol and polyaminoacids containing hydroxyl groups such as polyserine, polythreonine and polytyrosine as well as thiol containing polymers such as polycysteine are suitable. Col. 8, lines 12-15.

Moen is directed to dishwashing compositions. The polymers are added to the detergent composition to "enhance the overall performance of the dishwashing method. In

particular the addition of said polymers eliminates or reduces the deposition of the catalyst onto the articles in the wash." Col. 2, lines 25-31. This disclosure cannot possibly teach a "mucoadhesive polymer," as instantly claimed. Moreover, it does not teach a "mucoadhesive polymer comprising not more than 10 different monomers and at least one non-terminal thiol group." There is no teaching of having no more than 10 different monomers in the polymer. Nor is there any teaching of having at least one non-terminal thiol group.

The Moen reference further fails to disclose or suggest the dependent claims included in the rejection, *i.e.*, claims 28, 29 and 31-38. The passage cited in the Official Action, as set forth *supra*, makes no mention of having "at least 0.05 μmol of covalently bound thiol groups per gram of polymer" or "at least 0.1 μmol of covalently bound thiol," as recited in claims 28 and 29, respectively. Nor does the reference disclose having "at least one monomer having free thiol groups within said polymer," as recited in claim 33. Nor does the reference disclose or suggest a mucoadhesive polymer which exhibits total work of adhesion of more than 120 or 150 μJ to intestinal mucosa at pH 7, as recited in claims 34 and 35, respectively. Likewise, the reference fails to disclose or suggest mucoadhesive polymers having a TWA increase by at least 30%, 50% and 100% relative to a mucoadhesive polymer not containing a non-terminal thiol group, as claimed in claims 36-38, respectively. As such, Moen cannot anticipate these claims.

"To anticipate, every element and limitation of the claimed invention must be found in a single prior art reference, arranged as in the claim." *Brown v. 3M*, 265 F.3d 1349, 60

USPQ2d 1375 (Fed. Cir. 2001). Moen does not satisfy this requirement with respect to the instantly claimed invention. Moreover, as shown in the enclosed Declaration, a polymer which simply includes thiol groups will not be mucoadhesive. As such, Moen does not inherently teach or suggest the instantly claimed invention.

In view of the above, the prior art rejection is believed to be improper. Withdrawal of the rejection is respectfully requested and believed to be in order.

Claims 1 and 28-108 have also been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Bernkop-Schnürch et al (*Int. J. Pharm.* 157:17-25 (1997) and *Int. J. Pharm.* 146:247-54 (1997)) in view of Constancis. This rejection is respectfully traversed.

According to the Examiner, it would have been obvious to form a thiolated chitosan in view of the combined teachings of the references to obtain a composition with enhanced adhesive properties. Bernkop-Schnürch et al is said to teach mucoadhesive polymers comprising chitosan-antipain conjugates. Constancis is said to teach thiolating polymers to obtain improved bioadhesive properties.

Bernkop-Schnürch discloses mucoadhesive polymers; however, the reference fails to disclose or suggest polymers having thiol groups, as in the instantly claimed invention. Constancis is cited for his teaching of modification of biomaterials with thiolated compounds. However, as noted above, Constancis fails to disclose or even suggest modification of *mucoadhesive* polymers. There is no suggestion in Constancis to modify a

mucoadhesive polymer to contain at least one non-terminal thiol group. Constancis instead discloses bioadhesive substances having polysulfide crosslinking moieties.

As discussed *supra*, the polymers of Constancis are *not* mucoadhesive. Since Constancis is unrelated to mucoadhesive substances, there would be no motivation for the combination proposed in the Official Action. Since the Constancis polymers show no mucoadhesive properties, as shown by the enclosed Declaration, there would be no motivation for one skilled in the art to look to Constancis for a way to improve the mucoadhesive polymers. One skilled in the art would not be motivated to change the polymers of Bernkop-Schnürch and add thiol groups based on the disclosure of Constancis. *See,* Second Bernkop-Schnürch Declaration, Paragraph 30.

There would be no motivation to combine the teachings of Constancis, relating to bioadhesives, with the teachings of Bernkop-Schnürch et al, relating to mucoadhesives. Different principles are involved for these two types of polymers. The principle of binding of bioadhesives is based, according to Constancis, on a diffusion process of the monomers/oligomers into the tissue followed by a stabilizing polymerization process via oxidation of the thiol groups. This is similar to the principle used in other "super glues," such as glues based on cyanoacrylates which diffuse into surfaces and subsequently polymerize. The goal for bioadhesion is to achieve a very tight and strong connection of the bioadhesive with a given cell or tissue surface or to achieve a strong connection between cell or tissue surfaces. The "goal" for the compounds of Constancis is thus to adhere directly to the tissue.

By contrast, "mucoadhesion," as in Bernkop-Schnürch and the instant invention, is based on a different scientific concept. Mucus is a loosened, extremely wide meshed network which is characteristic for the mucus layers. A tight binding of a polymer molecule to the (tissue) surface adjacent to the mucus is, therefore, neither necessary nor desired for a mucoadhesive polymer. To the contrary, a covalent binding of the mucoadhesive polymer directly to the tissue surface could have extremely negative effects.

For example, a covalent binding of a perorally administered drug to the epithelial cells of the gastrointestinal tract would lead to an obstruction of bowels. Mucoadhesive polymers thus should specifically bind to the mucus layer above the tissue in these areas. With a mucus turnover of about 6-8 hours, the above-described effect (e.g., obstruction of bowels) is prevented by covalently linking the mucoadhesive polymers to the mucus rather than the tissue itself. Please note Figure 1 from Muller and Hildebrand, "Pharmazeutische Technologie: Moderne Arznelformen," Wissenschaftilche Veriagagesellschaft mbH Stuttgart (1997), Stuttgart, Germany, p. 280, previously submitted, which illustrates the adhesion of a mucoadhesive polymer to the mucus gel layer.

The compounds used by Constancis may be used *in vitro* or *in vivo* for binding biological tissues to each other or for binding a biological tissue and, e.g., an implanted biomaterial. The mucoadhesive polymers of the instant invention are intended to bind to the mucus gel layer and not to a tissue. This object of the bioadhesives as in Constancis is thus completely different from the object of mucoadhesive polymers, as described for applicants invention in the instant specification. *See, e.g.,* page 2, first paragraph. Thus,

there would have been no motivation for one skilled in the art to combine the cited art of Bernkop-Schnürch and Constancis as proposed in the Official Action.

As recognized by the Federal Circuit, there must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself. *In re Oetiker*, 24 USPQ2d 1443, 1446 (Fed. Cir. 1992). In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the examiner to provide a reason *why* one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Nesbit*, 25 USPQ2d 1817, 1819 (BPAI 1992). As stated above, in the present case, no such motivation exists.

The binding of the mucoadhesive polymers as claimed is based on a completely different and novel mechanism for mucoadhesion. Applicants' invention is based on the observation that the mucus consists of mucus glycoproteins, which are connected with each other via numerous disulfide bonds. By the addition of a thiolated mucoadhesive polymer, new disulfide bonds are formed via thiol/disulfide exchange reactions between the polymer and the mucus glycoproteins. This mechanism is illustrated in the previously submitted Figure 2, a copy of which is again enclosed for the Examiner's convenience. This mechanism has previously never been proposed or reported in the field of mucoadhesive polymers.

Prior to the instant invention, the formation of secondary bond formation was regarded as the principle source of mucoadhesion. *See, e.g.*, Hunt et al, *supra*. That carboxyl groups in their non-ionized form are capable of strong hydrogen bond formation was regarded as a substantial reason for the mucoadhesive properties of such substances. *See,* Hunt, p. 186, third paragraph, which states:

> In accordance with the theory that secondary bond formation is the principal source of mucoadhesion, those polymers with carboxyl groups present are all, without exception, mucoadhesive. The carboxyl group in its unionized form is capable of strong H-bond formation, and in its ionized form also able to interact electrostatically. However, the functional groups on the polymer backbone should not be in such close proximity that they interfere with each other (e.g. by intramolecular H-bonding). As the carboxyl concentration along a polymer chain decreases, for example, in moving from sodium alginate to Karya gum to gelatin, the mucoadhesive strength also decreases.

With respect to mucoadhesion, it is further stated that the direct interaction with the tissue or membrane surface is, in contrast with bioadhesion, not of relevance for mucoadhesion. *See, e.g.,* Hunt, p. 184, second paragraph, last sentence.

It should further be noted that *none* of the mucoadhesive polymers known in the art prior to the instant invention, as evidenced by Hunt, Table 1 and Figure 1, contained any thiol groups. This evidences that the role of thiol groups in the process of mucoadhesion was neither known nor proposed prior to applicants' invention. Even in mucoadhesive polymers based on proteins, no free thiol groups are present (such polymers would also have more than 10 different monomers). *See, e.g.,* Hunt, page 190, wherein the amino acid composition of gelatine is listed and cysteine residues are not even listed under amino acids with "low abundance." Moreover, as stated *supra*, the incorporation of thiol groups

into mucoadhesive polymers was deemed a "brilliant idea." *See, Pharmaceutical Research* and First Bernkop-Schnürch Declaration, ¶15.

Figure 1 of Hunt makes clear that the compounds regarded as the most potent mucoadhesive polymers in the prior art did not contain any thiol groups, much less "at least one non-terminal thiol group" as instantly claimed. It was thus surprising to applicants that by providing non-terminal thiol groups in such mucoadhesive polymers, the mucoadhesive properties of such polymers could be enormously improved. Indeed, the thiolated mucoadhesive polymers of the instant invention have mucoadhesion properties that are significantly superior to the best mucoadhesive polymers known in the art.

Therefore, even if Constancis taught bioadhesive polymers having non-terminal thiol groups, there would have been no motivation for one skilled in the art to incorporate thiol groups into mucoadhesive polymers to achieve the instant invention.

Moreover, even if the cited art were combined, unexpected results are achieved by the instant invention. As shown in the First Bernkop-Schnürch Declaration, unexpected results are achieved by incorporating non-terminal thiol groups into a mucoadhesive polymer. *See, e.g.,* First Bernkop-Schnürch Declaration, ¶¶13-15. That the TWA could increase 50 to over 100% by adding the non-terminal thiol groups would not have been expected.

For the Examiner's convenience, the Table of results showed as follows:

Polymer	Total work of adhesion in μJ; means ± SD (n= 3-8)	Reference
polycarbophil	110 ±28	A. Bernkop-Schnürch, V. Schwarz, S. Steininger, Polymers with thiol groups: a new generation of mucoadhesive polymers? Pharm. Res. 16 (1999) 876-881.
thiolated polycarbophil	280 ±68	
sodium carboxymethyl cellulose	108 ±17	A. Bernkop-Schnürch, S. Steininger, Synthesis and characterisation of mucoadhesive thiolated polymers, Int. J. Pharm. 194 (2000) 239-247.
thiolated sodium carboxymethyl cellulose	157 ±6	
chitosan HCl	23 ±10	C.E. Kast, A. Bernkop-Schnürch, Thiolated polymers: development and in vitro evaluation of chitosan-thioglycolic acid conjugates, Biomaterials 22 (2001) 2345-2352.
thiolated chitosan	234 ±0	
sodium alginate	26 ±1	A. Bernkop-Schnürch, C.E. Kast, M.F. Richter, Improvement in the mucoadhesive properties of alginate by the covalent attachment of cysteine, J. Control. Release 71 (2001) 277-285.
thiolated sodium alginate	102 ±36	

As shown in the Table, unexpected results in terms of the increase in total work of adhesion (TWA) is achieved by adding at least one non-terminal thiol group to a mucoadhesive polymer having not more than 10 different monomers. Such results as shown herein were not expected prior to the instant invention. As discussed *supra*, in the "Comments" regarding Applicant's draft of the manuscript to publish the results of the instant invention, Applicant's invention was deemed a "brilliant" idea.

In view of the above, the combination of references cannot be combined to achieve Applicant's claimed invention. Even if combined, the unexpected results of Applicant's invention is sufficient to overcome the rejection. Withdrawal of the rejection under §103(a) is thus respectfully requested. Such action is believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested. Such action is believed to be in order.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (650) 622-2360 so that prosecution of the application may be expedited.

Respectfully submitted,

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